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# Sleeping sickness in Uganda: a thin line between two fatal diseases

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## Abstract

**Objective** To determine, through the use of molecular diagnostic tools, whether the two species of parasite that cause human African trypanosomiasis have become sympatric.

**Design** Blood sampling of all available patients between June 2001 and June 2005 in central Uganda and between July and September 2003 in northwest Uganda and analysis of subcounty sleeping sickness records in Uganda between 1985 and 2005.

**Setting** Sleeping sickness treatment centres in central and northwest Uganda and in south Sudan.

**Participants** Patients presenting at the treatment centres and diagnosed as having sleeping sickness.

**Main outcome measure** Classification of parasites from patients from each disease focus as either *Trypanosoma brucei rhodesiense* (acute form) or *T b gambiense* (chronic form).

**Results** Blood from 231 patients with sleeping sickness in central Uganda and from 91 patients with sleeping sickness in northwest Uganda and south Sudan were screened for *T b rhodesiense* (detection of SRA gene) and *T b gambiense* (detection of TgsGP gene). All samples from central Uganda were classified as *T b rhodesiense*, and all samples from northwest Uganda and south Sudan were identified as *T b gambiense*.

**Conclusions** The two focuses of human African trypanosomiasis remain discrete, but the area of Uganda affected by the acute form of human sleeping sickness has increased 2.5-fold since 1985, spreading to three new districts within the past five years through movement of infected livestock. Without preventive action targeted at the livestock reservoir of this zoonotic disease, it is likely that the two disease focuses will converge. This will have a major impact on diagnosis and treatment of this neglected disease. Real time monitoring is recommended, using molecular diagnostic tools (at a regional surveillance centre, for example) targeted at both livestock and human patients.

## Introduction

Human African trypanosomiasis, or sleeping sickness, is responsible for an estimated 100 000 deaths every year.<sup>1</sup> Two pathogens are involved: *Trypanosoma brucei rhodesiense*, which causes an acute form of disease, and *T b gambiense*, the chronic form. *T b rhodesiense* is found in east Africa, and *T b gambiense* is present in central and west Africa.<sup>2</sup> Uganda represents a region of potential overlap, with the two focuses expanding towards each other.<sup>3–7</sup>

Sleeping sickness was first recognised in southeast Uganda in 1898 and in the north west of the country in 1902.<sup>8–9</sup> Refugee movements have spread *T b gambiense*

to form a contiguous focus with south Sudan,<sup>10–12</sup> raising the possibility that refugees may carry *T b gambiense* into areas endemic for *T b rhodesiense*.<sup>3</sup>

Animals were implicated in the transmission of *T b rhodesiense* disease during the 1940s epidemic in Busoga, southeast Uganda.<sup>13</sup> The disease re-emerged in Busoga between 1976 and 1983, when 19 974 patients had the disease diagnosed.<sup>14</sup> An outbreak of *T b rhodesiense* in Tororo district to the east of the Busoga focus in 1988 was brought under control by 1995 but not before 1180 cases had presented. Cattle restocking has been implicated in the latest outbreak of *T b rhodesiense* disease in 2000,<sup>15</sup> in which 18% of cattle were found to be carrying the human pathogen.<sup>16</sup> The disease has since spread to two adjacent districts<sup>17</sup>; the *T b rhodesiense* and *T b gambiense* focuses are predicted to merge, complicating diagnosis and treatment.<sup>1–18</sup>

Microscopy of blood, lymph, or cerebrospinal fluid informs treatment of *T b rhodesiense*. *T b gambiense* may not be evident by microscopy, and diagnosis is based on the card agglutination test for trypanosomiasis,<sup>19</sup> which is ineffective for diagnosis of *T b rhodesiense*. Drugs for the treatment of early stage disease differ<sup>20</sup>: pentamidine, the first line drug for *T b gambiense*, is not effective against early stage *T b rhodesiense*,<sup>21</sup> which is treated with suramin. Late stage cases of both diseases are treated with melarsoprol. The number of treatment failures of late stage *T b gambiense* is increasing; eflornithine is used in these cases but is not effective against late stage *T b rhodesiense*.<sup>1</sup> Overlap in the distribution of these parasites would complicate diagnosis and result in inappropriate treatment for critically ill patients.

We used molecular tools to examine the current distribution of the two parasite species in Uganda. Specifically, we observed the historical spread of disease in terms of land area affected and population at risk and identified sleeping sickness parasites from the two focuses.

## Methods

### Sleeping sickness and geographical area

Disease records for sleeping sickness across Uganda came from the Co-ordinating Centre for Trypanosomiasis in Uganda and from sleeping sickness treatment centres in affected regions. We obtained digital data for Uganda<sup>22</sup> from the geographical information system, ArcView 3.2 (Redlands, CA, USA) to determine the size of geographical areas affected through time. The administrative units shown on the map (figure) are districts, the highest administrative unit in Uganda. We determined the distribution of the

An appendix is on bmj.com



**Table 1** Molecular analysis of samples isolated from patients with confirmed sleeping sickness

	Result of gene screen			
Location	No of samples screened	HCGA positive*	TgsGP positive†	SRA positive‡
<b><i>T b rhodesiense</i> focus</b>				
Soroti district	210	210	0	210
Kaberaido district	19	19	0	19
Lira district	2	2	0	2
Total	231	231	0	231
<b><i>T b gambiense</i> focus</b>				
Arua district, West Nile	27	27	27	0
Kiri, south Sudan	21	21	21	0
Tambura, south Sudan	31	31	31	0
Ibba, south Sudan	12	12	12	0
Total	91	91	91	0
<b>Control</b>				
Akuem Bahr el Ghazal§	32	32	0	0

\*Human DNA present.

† *T b gambiense* DNA present.‡ *T b rhodesiense* DNA present.

§Region in Sudan unaffected by either form of human sleeping sickness.

disease at the level of the subcounty (a lower unit). We calculated the area of each region at risk from the total land area of the relevant administrative (district level) units and determined the population at risk from the 2002 national population and housing census.<sup>23</sup>

### Clinical samples

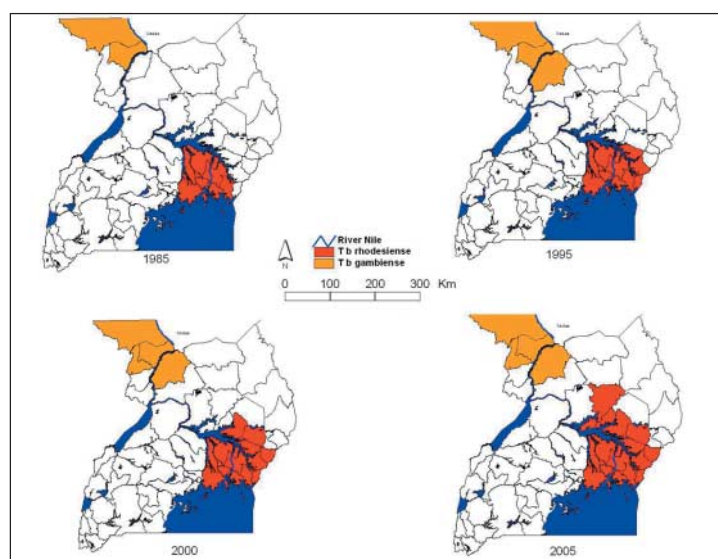
In southeast Uganda we obtained blood samples from 231 self reporting patients with sleeping sickness from Soroti, Kaberaido, and Lira districts who attended Serere Health Centre between June 2001 and June 2005 (Soroti: 2001 n=10, 2002 n=46, 2003 n=69, 2004 n=30, and 2005 n=55; Kaberaido: 2004 n=15, 2005 n=4; Lira 2004 n=1, 2005 n=1). We examined the samples to characterise the trypanosome parasites present (table 1).

In northwest Uganda and south Sudan we examined blood samples from 91 patients from the West Nile/south Sudan focus to characterise the parasites present in human blood. These comprised samples from 27 patients attending Omugo Health Centre, Arua District (West Nile region) and from 64 patients from three health centres in south Sudan (Kiri n=21, Ibba n=12, Tambura n=31) between July and September 2003 (table 1). We also collected samples from 32 pyrexia patients at Akuem Bahr el Ghazal, Sudan, outside the sleeping sickness focus, for use as negative control samples for both *T b rhodesiense* and *T b gambiense* (table 1).

We included all patients who presented for treatment during the study and were diagnosed as having sleeping sickness by clinic staff. The molecular tools used in this study were applied post hoc—the diagnosis of sleeping sickness was made in the relevant clinics according to standard protocols.

### Polymerase chain reaction analysis

Patients parasitologically positive for sleeping sickness were asked to provide a finger prick sample of blood, which was applied to a DNA binding matrix (FTA card, Whatman). The local health services obtained consent from patients, and agreement or otherwise did not compromise their access to treatment. We prepared FTA cards containing blood samples from sleeping



Sequential maps of areas of Uganda affected by sleeping sickness. *T b gambiense* (in orange) occurs in south Sudan and northwest Uganda, where substantial human population movements have occurred as a result of civil instability. *T b rhodesiense* (in red) has been spreading since the mid-1980s, and its transmission is now occurring within 150 km of the *T b gambiense* active focus. The tsetse belt for *Glossina fuscipes fuscipes* extends right across the region<sup>24</sup>

sickness patients for polymerase chain reaction (PCR) as previously described.<sup>25</sup> Full details of the PCR methods are provided in the appendix on bmj.com. Briefly, we firstly screened samples from all areas for the presence of human DNA (using human cytoskeletal gamma actin—HCGA), to confirm that the sample contained suitable DNA for PCR amplification. We screened all samples with generic *Trypanozoon* primers to identify the presence of *T brucei* sl DNA.<sup>26</sup> We screened all *Trypanozoon* positive samples for *T b gambiense* (with primers for TgsGP<sup>27, 28</sup>) and *T b rhodesiense* (with primers for the human serum associated gene SRA<sup>16, 29</sup>). We separated PCR products by agarose (1.5%) electrophoresis containing ethidium bromide (0.2 µg/ml) and visualised them on an ultraviolet transilluminator.

### Results

Since the mid-1980s, the area of Uganda affected by *T b rhodesiense* sleeping sickness has increased by a factor of 2.5, from 13 820 km<sup>2</sup> to 34 843 km<sup>2</sup>, and the population at risk from *T b rhodesiense* has doubled (table 2). Before 1985, sleeping sickness in east Uganda was restricted to districts clustered around the north shore of Lake Victoria and the source of the Nile (the traditional Busoga focus). During an epidemic that started in the late 1980s the disease spread eastwards into Tororo and Busia districts, with sporadic cases in Pallisa and Mbale districts on the Uganda-Kenya border. This epidemic in Tororo district was brought under control in the mid-1990s. However, from 1998 onwards, cases of sleeping sickness were detected in Soroti district, much further to the north; the spread of this new epidemic area was attributed to the movement of the reservoir host (domestic cattle) as a result of restocking activities in the region. Control activities that sought to contain this epidemic were largely

**Table 2** Proportional increase in area affected by *T b rhodesiense* sleeping sickness in southeast Uganda, 1985-2005

Year	Area affected (km <sup>2</sup> )	Proportional increase since 1985
1985	13 820	1.00
1995	18 420	1.33
2000	26 019	1.88
2005	34 843	2.52

unsuccessful,<sup>15 30</sup> and the disease, having become established in Soroti district, has spread further still to Kaberamaido district and more recently to the southern edge of Lira district.<sup>17</sup> At the same time, population movements as a result of civil instability on the Sudanese border resulted in expansion of the *T b gambiense* focus. The affected districts in the two disease focuses are now approximately 150 km apart (fig).

We positively identified *T b gambiense* alone in blood from all 91 patients with sleeping sickness from the *T b gambiense* focus, which included patients presenting in Arua district (West Nile region), north Uganda, and from health centres in south Sudan (table 1). None of these samples from this sleeping sickness focus was amplified by the gene marker SRA specific for *T b rhodesiense*, confirming that all patients examined were infected with *T b gambiense* parasites. Of the 231 samples obtained from the *T b rhodesiense* sleeping sickness outbreak in east Uganda between 2001 and 2005, all amplified the SRA gene for *T b rhodesiense*, showing that all these patients, presenting from Soroti, Kaberamaido, and Lira, were infected with *T b rhodesiense* and confirming SRA as a diagnostic marker for *T b rhodesiense* sleeping sickness in East Africa.<sup>16</sup> We saw no amplification in any sample from Soroti, Kaberamaido, or Lira with TgsGP, confirming that this gene specific for *T b gambiense* is not present in people presenting with sleeping sickness in this region (table 1).

The results presented here suggest that the parasites circulating in these two disease focuses remain discrete and confirm that the disease outbreaks in Kaberamaido and Lira are attributable to *T b rhodesiense* (acute form of sleeping sickness), confirming the recent expansion of the *T b rhodesiense* focus. None of the 32 samples from pyrexial patients from Akuem Bahr el Ghazal in Sudan, outside the sleeping sickness focuses, that were HCGA positive for human DNA were infected with *T brucei* sl.

## Discussion

### Risk of overlap

Control activities aimed at containing *T b rhodesiense* in east Uganda have been largely ineffectual.<sup>15 17 30</sup> Civil instability in the region and a lack of control measures to contain the spread of disease (such as targeting the animal reservoir by restricting through cattle movements) have resulted in cases of sleeping sickness occurring further and further northwards, closer to the *T b gambiense* endemic area.

The *T b gambiense* sleeping sickness focus in north-west Uganda seems to be relatively stable, but the long

asymptomatic stage associated with this disease means that, without active surveillance of the human reservoir population, this parasite could spread with movements of displaced peoples in the region. In south Sudan, the absence of disease control activities for eight years after civil disturbance saw the expansion of that sleeping sickness focus and some extremely high disease prevalences (for example, 29% at Ibbe, Marindi County<sup>10</sup>).

We have shown, using molecular tools, that the cases of sleeping sickness in Kaberamaido and Lira districts of Uganda are indeed due to *T b rhodesiense*. Although a real risk of overlap with the *T b gambiense* sleeping sickness focus remains, we found no evidence to indicate that the two active disease focuses have yet converged—that is, there is no *T b rhodesiense* within the *T b gambiense* sleeping sickness focus or vice versa. However, the area currently at risk from *T b rhodesiense* does now overlap with a region affected by a *T b gambiense* outbreak in 1957.<sup>31</sup> The active *T b rhodesiense* disease focus is now only 150 km from areas currently affected by *T b gambiense* in the north west of Uganda.

The risk of sleeping sickness spreading by means of the livestock reservoir host continues to be a public health challenge. If infected cattle continue to be traded northwards in the absence of control measures then overlap of the two disease focuses will inevitably occur. If and when overlap does occur, a rapid response including revision of established diagnostic and treatment protocols will be needed to minimise its impact. Such a surveillance programme may be difficult to sustain owing to the unstable nature of the civil situation in this part of the country.<sup>28</sup> Currently, livestock for sale in Uganda are required to be treated at their point of origin or before sale; this forms part of the national policy for trypanosomiasis control, although it has been difficult to implement at local level.<sup>30</sup> Given the high cost of treating patients and implementing active screening programmes in new regions with limited human health resources, strengthening this policy and encouraging its enforcement by district authorities would seem appropriate.

Economic analysis suggests that the financial benefits of treating the animal reservoir for *T b rhodesiense* sleeping sickness would more than cover the costs of treatment and may even result in a negative cost per disability adjusted life year averted. Treating cattle increases income from livestock, as the trypanocidal drugs used to clear infection are effective against the trypanosomes that are pathogenic to cattle as well as zoonotic *T b rhodesiense*. Lowering the incidence of sleeping sickness by treating the animal reservoir will reduce future costs of treating human patients.<sup>32</sup> A transsectoral assessment of costs and benefits for control of zoonotic *T b rhodesiense*, as has been done for control of brucellosis, would seem appropriate.<sup>33</sup> Sleeping sickness tends to affect the poorest and most disenfranchised rural communities with the least access to health care. Public health messaging and extension services are urgently needed to improve knowledge and reporting of these diseases.



## What is already known on this topic

Two pathogens can cause sleeping sickness: *Trypanosoma brucei rhodesiense*, found in east Africa, and *T b gambiense*, found in central and west Africa

Uganda represents a region of potential overlap between the two focuses

## What this study adds

The two sleeping sickness focuses in Uganda are discrete and have not yet overlapped

They are, however, steadily converging and are now only 150 km apart

## Recommendations

Surveillance activities should be put in to place to monitor the situation, so that any overlap in disease distribution can be detected at the earliest opportunity. As the parasites involved in *T b gambiense* and *T b rhodesiense* sleeping sickness are morphologically identical, such monitoring will inevitably require screening of blood samples and differentiation of the parasites with the molecular methods described here. Although these tools are not yet available at the bedside or pen-side, the technologies described here are applicable to a suitably equipped in-country regional laboratory targeted at both livestock and human patients at the leading edge of the sleeping sickness focuses.<sup>17 26 29</sup> The continent-wide importance of these two parasite species overlapping is such that a properly equipped screening laboratory and staff training should be set up as a matter of urgency. This might take the form of an internationally funded and locally managed facility under the supervision of the relevant authorities in Uganda. Given the economic impact of trypanosomiasis on both the livestock and human health sectors,<sup>34</sup> this would be a cost effective proposal for management of this neglected zoonotic disease.

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